Methylphenidate-Induced Chorea Due to Possible Cytochrome P450 metabolism Heterogeneity: A Rare Case

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Introduction
Chorea is defined as a hyperactive movement disorder associated with inculcary, quick, and unpredictable muscle contractions of the limbs, face, and trunk. The unpredictable nature of these movements includes variation in speed, timing, and direction of movement. Many potential causes may be linked with chorea including autoimmune processes, infections, hypoergic or ischemic injuries, mitochondrial diseases, and toxins. It has been suggested that the excessive dopaminergic activation in corpus striatum, caudate or putamen are largely responsible for choreiform movements. A wide variety of medications and illicit drugs have been associated with movement disorders. Examples include a multitude of antipsychotic drug induced movement disorders and dyskinesia related to dopaminergic agents, like levodopa and metoclopramide.

Dyskinesia have been associated with psychostimulant use, such as methylphenidate (RitalinTM, ConcertaTM). However, most cases reported were associated with large doses or chronic use.

Aside from dyskinesia, Methylphenidate is known to be associated with its dose, tremor, and muscle spasm. Adverse effects of Methylphenidate include anxiety, hyperactivity, euphoria, abnormal movements, and psychiatric dysregulation.

These effects are mediated through dopamine and norepinephrine reuptake inhibition. Additionally, there is an apparent increase in cerebral cortex and subcortical structure stimulation, similar to that seen in amphetamine use.

This case is unlike usual cases of the methylphenidate induced movement disorders as patient has no movement disorder when she was on methylphenidate alone for 2 years in the past.

This case considers the interaction of methylphenidate in the presence of a choreiform P450 2D6 and 3A4 inhibitor such as methylphenidate, paroxetine and how this may lead to chorea.

Case Presentation
A 47-year-old female was admitted to our hospital after presenting to the emergency department with 1 week of involuntary arm and leg movements.

Patient had a history of anxiety and opioid use disorder. She was on 110 mg of methadone for the last 11 months for opioid use disorder and was recently started on paroxetine 10 mg daily for anxiety.

After a recent visit to a neurologist where she disclosed that she had a history of ADHD and had been formerly treated with methylphenidate (of an unknown dose), she was restarted on methylphenidate 20 mg BID.

The baseline failing movements started acute after two days of initiating methylphenidate in addition to her chronic methylphenidate treatment, as well as a two-week period of initiation of paroxetine. The choreiform movements were violent enough to cause an arm fracture.

Lab work showed normal CBC, CMP, HbRPL, CRP, CK, and TSH. Urine drug screen, CT angiography of the head, and Huntington’s disease testing were all-unremarkable, suggesting a decreased likelihood of illicit drugs, traumatic brain injury, or Huntington’s Disease etiologies.

Neurology consult confirmed the diagnosis as drug induced chorea.

The patient was on methadone alone for eleven months and methylphenidate alone two years ago with no involuntary movements or any similar presentation.

Patient’s choreoid movements disappeared after discontinuation of methylphenidate and IV benadryl.

Patient was educated and encouraged to hold off on methylphenidate if she decides to continue methylphenidate and paroxetine.

Discussion
This is a very complicated case where patient was independently on methadone and methylphenidate at different time periods with no abnormal movements, but with the combination, including an SSR1 triggered basal choral movements. Risk factors for development of chorea following methylphenidate administration are unclear.

It prompts an important question about possible drug-drug interactions between the methylphenidate, methadone and paroxetine that might have triggered the abnormal movements.

Although higher doses and chronic use of methylphenidate may be related to adverse effects, some other unknown factors must also be playing a role. Methylphenidate inhibits dopamine reuptake by binding to the dopamine transport complex leading to increased synaptic dopamine concentration, mainly in the striatum.

Methylphenidate, like other psychostimulants, are thought to cause motor symptoms through their extracellular increase of dopamine and norepinephrine.

Reports regarding the effect of methylphenidate (MPH) on the choreiform P450 (P450) system are sparse.

The main enzyme responsible for Ndemethylation of methadone is CYP2D6, with lesser involvement from CYP1A2 and CYP2D6. CYP2B6 may play a significant role in metabolism as well.

Significant CYP2D6 inhibition is associated with paroxetine, which appears to result in a clinically relevant drug interaction with methadone; however, paroxetine’s CYP3A4 inhibition in vivo is not believed to be significant.

CYP2D6 is also significantly involved in the biotransformation of methadone. The polymorphic nature of CYP2D6 must therefore be considered a variable in drug interactions, particularly those associated with methadone.

References
9. Ozgul Erim, Cemrer Yeslam, Sven Ayse Ipek Bag, Nazan Ekin, Ozge Ipek Dogan, Methylphenidate-induced Encephalopathy of Chorea in a Child Resolved with Switching to SSRI, methylphenidate, and a cytochrome P450 inhibitor, methylphenidate.

Take Home Points
- Even though the combination of methylphenidate, methadone and SSR1 is a common practice, the occurrence of choreiform movements in this very rare case might be due to the heterogeneity and polymorphism of the cytochrome P450 enzymes in this patient.
- Polymorphisms of the structural genes are common, leading to wide inter-individual and ethnic differences in drug metabolism.
- This case challenges physicians to broaden their differential diagnosis for acute onset of choreiform movement disorders. This unique case intrigues the thought process to consider the role of cytochrome P450 end metabolism causing interaction between SSR1, methylphenidate, and a cytochrome P450 inhibitor, methylphenidate.